

**PRODUCT NAME**

Utraphen Film Coated Tablets 37.5mg/325mg

**DOSAGE FORMS AND STRENGTHS**

It occurs as a light yellow capsular shaped, biconvex film-coated tablet, branded "755" on one side and "STD" on the other side.

Each film coated tablet contains 37.5 mg tramadol hydrochloride and 325 mg paracetamol.

**CLINICAL INFORMATION****Indications**

Utraphen is indicated for the management of moderate to severe pain.

**DOSAGE AND ADMINISTRATION****Dosage****Adults and children 16 years of age and over**

The maximum single dose of Utraphen is 1 to 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day. The lowest effective dose should be used for the shortest period of time.

**Adults and adolescents (12 years and older)**

Utraphen is not approved for use in patients below 12 years old.

**Paediatric population**

The safety and efficacy of Utraphen has not been studied in the paediatric population. Therefore, use of Utraphen is not recommended in patients under 12 years of age.

**Treatment withdrawal**

Do not stop use of Utraphen abruptly. Withdrawal symptoms may be relieved by tapering the medication (see *Warnings and Precautions – Treatment Withdrawal*).

**Special populations****Children below 16 years of age**

The use of Utraphen is contraindicated in children below 12 years of age (see *Contraindications*).

The safety and effectiveness of Utraphen in children aged 12 to below 16 years of age has not been established (See *Contraindications and Warnings and Precautions - Other Risk Factors for Life-threatening Respiratory Depression in Children*).

**Elderly (65 years of age and older)**

No overall differences with regard to safety or pharmacokinetics were noted between patients  $\geq 65$  years of age and younger patients. However, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, of concomitant disease and multiple drug therapy.

**Renal impairment**

In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of Utraphen be increased not to exceed 2 tablets every 12 hours.

**Hepatic impairment**

The use of Utraphen in patients with severe hepatic impairment is not recommended.

**Administration**

Utraphen tablets are for oral administration.

Utraphen can be administered without regard to food.

**Contraindications**

Utraphen is contraindicated:

- in all children younger than 12 years of age.
- in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- in patients who have previously demonstrated hypersensitivity to tramadol, paracetamol, any other component of this product or opioids.
- in cases of acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs.

- in patients using monoamine oxidase inhibitors (MAOIs) concurrently or within the last 14 days.
- in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.
- in patients with significant respiratory depression (see *Warnings and Precautions*).

## Warnings and Precautions

### WARNING

**This preparation contains PARACETAMOL.**

**Do not take any other paracetamol containing medicines at the same time.**

**Allergy alert:** Paracetamol may cause severe skin reactions. Symptoms may include skin reddening, blisters or rash.

These could be signs of a serious condition. If these reactions occur, stop use and seek medical assistance right away.

### Seizures

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking serotonergic drugs including: selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics), tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or opioids.

Administration of tramadol may enhance the seizure risk in patients taking: monoamine oxidase inhibitors (MAOIs), neuroleptics or other drugs that reduce the seizure threshold.

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, central nervous system [CNS] infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

### Anaphylactic reactions

Patients with a history of anaphylactic reactions to codeine and other opioids may be at increased risk and therefore should not receive Ultraphen.

Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with tramadol.

Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction.

### Paediatric population

The safety and efficacy of Ultraphen has not been studied in the paediatric population. Therefore, use of Ultraphen is not recommended in patients under 12 years of age.

### Respiratory depression

Patients with significant respiratory depression (see *Contraindications*) or acute, severe bronchial asthma are at increased risk of life-threatening respiratory depression when treated with opioids.

Administer Ultraphen cautiously in patients at risk for respiratory depression, including patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression, as in these patients, even therapeutic doses of Ultraphen may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered.

When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.

Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia) (see *Adverse Reactions*).

Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids. (see *Dosage and Administration, Treatment Withdrawal; Warnings and Precautions, Treatment Withdrawal*).

### Cytochromes P450 (CYP) 2D6 ultra-rapid metabolism

Some individuals may be CYP2D6 ultra-rapid metabolisers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolites O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression. (see section *Overdose - Symptoms and signs, Tramadol*)

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16-28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

Alternative medication, dose reduction and/or increased monitoring for signs of tramadol overdose, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolizers. (see *Pharmacokinetic Properties*). Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) (see *Overdose - Symptoms and signs, Tramadol*).

#### **Other risk factors for life-threatening respiratory depression in children**

Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol is subject to variability in metabolism based upon CYP2D6 genotype, which can lead to increased exposure to an active metabolite. Based upon postmarketing reports with tramadol, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol (see *Contraindications*). Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect (see *Contraindications*). Because of the risk of life-threatening respiratory depression and death, avoid the use of Utraphen in adolescents younger than 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea and concomitant use of other medications that cause respiratory depression.

As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of opioid overdose (see *Dosage and Administration and Overdose - Symptoms and signs, Tramadol*).

#### **Use with Central Nervous System (CNS) depressants, including alcohol**

The concomitant use of tramadol (an active ingredient in Utraphen) with CNS depressants, including alcohol, may cause additive CNS depressant effects, including profound sedation and respiratory depression. Utraphen should be used with caution and in reduced dosages when administered to patients receiving CNS depressants. (see *Interactions*)

Utraphen should be used with caution in patients with increased intracranial pressure or head injury.

#### **Drug dependence and potential for abuse**

Utraphen contains tramadol as an active ingredient. A portion of the analgesic effect of Utraphen is attributable to the binding of the active ingredient, tramadol, to the mu-opioid receptor. Upon repeated administration of opioids, tolerance, physical dependence, and psychological dependence may develop, even at recommended dosages. Assess each patient's risk for opioid dependence and abuse prior to prescribing Utraphen and monitor all patients receiving Utraphen for development of these behaviors. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression).

Utraphen should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids.

#### **Increased risk of hepatotoxicity with alcohol use**

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive paracetamol use.

#### **Treatment withdrawal**

Withdrawal symptoms may occur if Utraphen is discontinued abruptly. Panic attacks, severe anxiety, hallucinations, paresthesia, tinnitus, and unusual CNS symptoms have also been very rarely reported with abrupt discontinuation of tramadol hydrochloride. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.

#### **Serotonin syndrome with concomitant use of serotonergic drugs**

Use Utraphen with great caution in patients taking serotonergic drugs including SSRIs. Concomitant use of tramadol with serotonergic drugs including SSRI's increases the risk of adverse events, including seizure and serotonin syndrome (see *Interactions*).

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of Utraphen with serotonergic drugs (see *Interactions with Other Medicaments*). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (see *Interactions with Other Medicaments*). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Utraphen if serotonin syndrome is suspected.

#### **Adrenal insufficiency**

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

#### **Sexual function/ reproduction**

Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see *Postmarketing Experience*).

## Renal impairment

Utraphen has not been studied in patients with impaired renal function. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of Utraphen be increased not to exceed 2 tablets every 12 hours. Utraphen is not recommended in patients with creatinine clearance of less than 10 mL/min.

## Hepatic impairment

The use of Utraphen in patients with severe hepatic impairment is not recommended.

## Serious Skin Reactions

Rarely, paracetamol may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens – Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

## Hyponatremia

Hyponatremia has been reported very rarely with the use of Utraphen usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatremia. In some reports, this hyponatremia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of Utraphen and appropriate treatment (e.g. fluid restriction). During Utraphen treatment, monitoring for signs and symptoms of hyponatremia is recommended for patients with predisposing risk factors.

## Precautions general

The recommended dose of Utraphen should not be exceeded.

Utraphen should not be co-administered with other tramadol or paracetamol-containing products.

## Risks from Concomitant Use with Benzodiazepines

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Utraphen with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Utraphen is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (see *Interactions*).

## Interactions

Based on its pharmacodynamic and pharmacokinetic properties, tramadol and paracetamol exhibits a potential for pharmacodynamic and pharmacokinetic interactions. The various types of interaction, associated general recommendations and lists of examples are described below. These lists of examples are not comprehensive and therefore it is recommended that the label of each drug that is co-administered with tramadol and paracetamol be consulted for information related to interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

**Table 1. Drug Interactions with Utraphen**

<b>Inhibitors of CYP2D6</b>	
<i>Mechanism:</i>	Enzyme inhibition resulting in decreased rate of metabolism of tramadol
<i>Clinical Impact:</i>	The concomitant use of Utraphen and CYP2D6 inhibitors may result in an increase in the plasma concentration of tramadol and a decrease in the plasma concentration of M1, particularly when an inhibitor is added after a stable dose of Utraphen is achieved. Since M1 is a more potent $\mu$ -opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome. After stopping an inhibitor of CYP2D6, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease and the M1 plasma concentration will increase which could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity, and may cause potentially fatal respiratory depression (see <i>Pharmacological Properties – Pharmacokinetic properties</i> ).
<i>Intervention:</i>	If concomitant use of an inhibitor of CYP2D6 is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome (see Warnings and Precautions – CYP2D6 ultra rapid metabolism of tramadol).

	If an inhibitor of CYP2D6 is discontinued, consider lowering Ultraphen dosage until stable drug effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.
<i>Examples</i>	Quinidine, fluoxetine, paroxetine, amitriptyline and bupropion
<b>Inhibitors of CYP3A4</b>	
<i>Mechanism:</i>	Enzyme inhibition resulting in decreased rate of metabolism of tramadol
<i>Clinical Impact:</i>	The concomitant use of Ultraphen and an inhibitor of CYP3A4 can increase the plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1. After stopping an inhibitor of CYP3A4, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease, resulting in decreased opioid efficacy and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.
<i>Intervention:</i>	If concomitant use is necessary, consider dosage reduction of Ultraphen until stable drug effects are achieved. Follow patients closely for increased risk of serious adverse events including seizures and serotonin syndrome, and adverse reactions related to opioid toxicity including potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Ultraphen is achieved. If an inhibitor of CYP3A4 is discontinued, consider increasing the Ultraphen dosage until stable drug effects are achieved and follow patients for signs and symptoms of opioid withdrawal.
<i>Examples</i>	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
<b>CYP3A4 Inducers</b>	
<i>Mechanism:</i>	Enzyme induction resulting in increased rate of metabolism of tramadol.
<i>Clinical Impact:</i>	The concomitant use of Ultraphen and an inducer of CYP3A4 can decrease the plasma concentration of tramadol, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol. After stopping an inducer of CYP3A4, as the effects of the inducer decline, the tramadol plasma concentration will increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, seizures and serotonin syndrome.
<i>Intervention:</i>	If concomitant use is necessary, consider increasing the Ultraphen dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal. If an inducer of CYP3A4 is discontinued, consider Ultraphen dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression. Patients taking carbamazepine, an inducer of CYP3A4, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of Ultraphen and carbamazepine is not recommended.
<i>Examples</i>	Rifampin, carbamazepine, phenytoin
<b>Benzodiazepines and Other Central Nervous System (CNS) Depressants including alcohol</b>	
<i>Mechanism:</i>	Additive or synergistic pharmacodynamic effect
<i>Clinical Impact:</i>	The concomitant use of tramadol with central nervous system depressants, such as benzodiazepines and other sedatives/hypnotics, anesthetic agents, phenothiazines, tranquilizers, opioids or alcohol, may produce additive CNS depressant effects, such as profound sedation and respiratory depression. If concomitant use of Ultraphen with a CNS depressant is clinically necessary, prescribe the lowest effective dosages and minimum duration for both drugs, and follow patients closely for signs of respiratory depression. <u>Benzodiazepines</u> Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma, and death. The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at $\mu$ -receptors, and benzodiazepines interact at GABA <sub>A</sub> sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
<i>Intervention:</i>	<u>Benzodiazepines</u> Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions). Limit dosages and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.
<b>Serotonergic Drugs</b>	
<i>Mechanism:</i>	Additive or synergistic pharmacodynamic effect
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Ultraphen if serotonin syndrome is suspected.
<i>Examples</i>	Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT <sub>3</sub> receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol) monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (see Warnings and Precautions).
<b>Monoamine Oxidase Inhibitors (MAOIs)</b>	
<i>Mechanism:</i>	Additive or synergistic pharmacodynamic effect
<i>Clinical Impact:</i>	The concomitant use of Ultraphen with MAOIs, or use within 14 days of their discontinuation, is contraindicated due to the increased risk of seizures and serotonin syndrome (see Contraindications). MAOI interactions with opioids may manifest as serotonin syndrome (see Warnings and Precautions – use with serotonin reuptake inhibitors) or opioid toxicity (e.g., respiratory depression, coma) (see Warnings and Precautions –Respiratory Depression).
<i>Intervention:</i>	Do not use Ultraphen in patients taking MAOIs or within 14 days of stopping such treatment.

<i>Examples</i>	phenelzine, tranylcypromine, linezolid
<b>Warfarin</b>	
<i>Clinical Impact:</i>	As medically appropriate, periodic evaluation of prothrombin time should be performed when Ultraphen and these agents are administered concurrently due to reports of increased International Normalized Ratio (INR) in some patients. Post-marketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times. There have been several reports that suggest that paracetamol may produce hypoprothrombinemia when administered with warfarin-like compounds.
<i>Intervention:</i>	Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.
<b>Cimetidine</b>	
<i>Clinical Impact:</i>	Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.

### **Pregnancy, Breast-feeding and Fertility**

#### **Pregnancy**

Tramadol has been shown to cross the placenta. There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has not been established. Ultraphen is not recommended for pregnant women.

The use of opioids during childbirth might result in respiratory depression in the newborn infant.

Prolonged use of Ultraphen, or other opioids, during pregnancy may lead to neonatal opioid withdrawal syndrome. This risk is particularly increased during the last trimester of pregnancy.

#### **Breast-feeding**

Ultraphen is not recommended for breast-feeding mothers because its safety in infants and newborns has not been studied.

Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of O-desmethyltramadol (M1). At least one death was reported in a breast-feeding infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. A baby breast-feeding from an ultra-rapid metabolizer mother taking Ultraphen could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breast-feeding is not recommended during treatment with Ultraphen.

Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

#### **Fertility**

The effect of tramadol or tramadol/paracetamol combination on human fertility has not been evaluated.

#### **Effects on Ability to Drive and Use Machines**

Ultraphen may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

#### **Adverse Reactions**

Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported.

<b>System Organ Class</b>	<b>Adverse Reaction</b>
Respiratory system	Rare: Respiratory depression
Metabolism and nutrition disorders	Not known: Hyponatremia/syndrome of inappropriate antidiuretic hormone
Immune system disorders	Very rare: Fixed eruption
Serotonin syndrome (Postmarketing Experience)	see Warnings and Precautions
Adrenal insufficiency (Postmarketing Experience)	see Warnings and Precautions

#### Postmarketing Experience

##### *Androgen deficiency*

Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The casual role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

##### *Infertility*

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

#### **Overdose**

##### **Accidental ingestion**

Accidental ingestion of tramadol can result in respiratory depression and seizures due to an overdose of tramadol. Respiratory depression and seizures have been reported in a child following ingestion of a single tablet.

Fatalities due to tramadol overdose have also been reported.

### Symptoms and signs

Utraphen is a combination product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, paracetamol toxicity or both. The initial symptoms of tramadol overdose may include respiratory depression and/or seizures. The initial symptoms seen within the first 24 hours following an paracetamol overdose may include: gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

### Tramadol

Serious potential consequences of overdosage of the tramadol component are respiratory depression, lethargy, coma, seizure, cardiac arrest and death. In addition, cases of QT prolongation have been reported during overdose.

### Paracetamol

Paracetamol in massive overdosage may cause hepatic toxicity in some patients. Early symptoms following a potentially hepatotoxic overdosage may include: gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor, and diaphoresis. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

### Treatment

A single or multiple overdose with Utraphen may be a potentially lethal polydrug overdose, and appropriate expert consultation, if available, is recommended.

While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. Based on experience with tramadol, hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

In treating an overdosage of Utraphen, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center (where available) to determine the latest recommendations for the management of an overdose. Hypotension is usually hypovolemic in etiology and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted when necessary, to provide assisted respiration.

In adult and pediatric patients, any individual presenting with an unknown amount of paracetamol ingested or with a questionable or unreliable history about the time of ingestion should have a plasma paracetamol level drawn and be treated with acetylcysteine. If an assay cannot be obtained and the estimated paracetamol ingestion exceeds 7.5 to 10 grams for adults and adolescents or 150mg/kg for children, dosing with N-acetylcysteine should be initiated and continued for a full course of therapy.

## PHARMACOLOGICAL PROPERTIES

### Chemical names

Tramadol hydrochloride  
(±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

### Paracetamol

N-acetyl-p-aminophenol (4-hydroxyacetanilide).

### Pharmacodynamic Properties

Pharmacotherapeutic group: Analgesics, Opioids in combination with non-opioid analgesics, ATC code: N02AJ13

### Pharmacodynamic effects

Tramadol is a centrally acting analgesic compound. At least two complementary mechanisms appear applicable, binding of parent and M1 metabolite to  $\mu$ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Paracetamol is another centrally acting analgesic. The exact site and mechanism of its analgesic action is not clearly defined.

When evaluated, the combination of tramadol and paracetamol exhibited a synergistic effect.

### Pharmacokinetic Properties

#### General

Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. Tramadol has a slower absorption and longer half-life when compared to paracetamol.

After a single oral dose of one Tramadol/Paracetamol combination tablet (37.5 mg/325 mg) peak plasma concentrations of 64.3/55.5 ng/mL [(+)-Tramadol/(-)-Tramadol] and 4.2  $\mu$ g/ml (paracetamol) are reached after 1.8 h [(+)-Tramadol/(-)-Tramadol] and 0.9 h (Paracetamol), respectively. Mean elimination half-lives  $t_{1/2}$  are 5.1/4.7 h [(+)-Tramadol/(-)-Tramadol] and 2.5 h (paracetamol).

Single and multiple dose pharmacokinetic of Utraphen showed no significant drug interactions between tramadol and paracetamol.

#### Absorption

Tramadol hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of tramadol tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two Utraphen tablets occurs at approximately two and three hours, respectively, post-dose in healthy adults.

Oral absorption of paracetamol following administration of Utraphen is rapid and almost complete and occurs primarily in the small intestine. Peak plasma concentrations of paracetamol occur within 1 hour and are not affected by co-administration with tramadol.

#### Food effects

The oral administration of Utraphen with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol, so that Utraphen can be taken independently of meal times.

#### Distribution

The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20%.

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg.

A relative small portion (~20%) of paracetamol is bound to plasma protein.

#### **Metabolism**

Plasma concentration profiles for tramadol and its M1 metabolite measured following dosing of Utraphen showed no significant change compared to dosing with tramadol alone.

Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be N- and O- demethylation and glucuronidation or sulfation in the liver. Tramadol is extensively metabolized by a number of pathways, including CYP2D6. Patients who are CYP2D6 ultra-rapid metabolizers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients (see Warnings and Precautions - CYP2D6 Ultra-Rapid Metabolism of Tramadol). The prevalence of this CYP2D6 genotype varies by population and has been reported in literature to range from 1% to 10% in African Americans, Caucasian Americans, Asians and Europeans (including specific studies in Greeks, Hungarians and Northern Europeans) to as high as 29% in African/Ethiopians.

Paracetamol is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:

- a) conjugation with glucuronide;
- b) conjugation with sulfate; and
- c) oxidation via cytochrome P450 enzyme pathway.

#### **Excretion**

Tramadol and its metabolites are eliminated primarily by the kidney. The plasma elimination half- lives of racemic tramadol and M1 are approximately six and seven hours, respectively. The plasma elimination half-life of racemic tramadol increased from approximately six hours to seven hours upon multiple dosing of Utraphen.

The half-life of paracetamol is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Paracetamol is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of paracetamol is excreted unchanged in the urine.

#### **Incompatibilities**

None known

#### **Storage Conditions**

Store below 30°C in the original package. Keep out of reach of children.

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store Utraphen securely, in a location not accessible by others.

#### **Nature and Contents of Container**

Utraphen tablets are packaged in PVC/Alu blister, 10 tablets per blister, and 10 blisters with 1 package insert per printed individual box.

#### **Instructions for Use and Handling and Disposal**

Any unused Utraphen should be disposed of in accordance with local requirements.

#### **MANUFACTURER**

**STANDARD CHEM. & PHARM. CO., LTD.**

6-20, Tuku, Tuku Village,

Sinying District, Tainan City 73055, Taiwan.

#### **DATE OF REVISION OF THE TEXT**

20/06/2022